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DOCUMENT-IDENTIFIER: US 5874567 A
TITLE: Therapeutic oligonucleotides targeting the human MDR1 and MRP genes

Brief Summary Text (8):
First, most chemical inhibitors used clinically to combat multidrug resistance have serious side effects unrelated to their ability to inhibit P-gp. In contrast, the phosphorothioate oligo, OL(1)p53, has been found to be essentially devoid of any toxicity when administered to patients (Bayever et al., Antisense Res. Dev. 2: 109-110, 1992; Antisense Res. Dev., in press, 1994). Similarly, this and other phosphorothioates have been shown to be nontoxic to a variety of animal species, even when given at high doses (Cornish et al., Pharmacol. Com. 3: 239-247, 1993; Crooke, Ann. Rev. Pharm. Toxicol. 32: 329-376, 1992; Iversen, Anti-Cancer Drug Design 6: 531-538, 1991). These findings show that at least some types of oligo have no acute toxicity per se when given systemically to animals or patients.

Brief Summary Text (11):
Furthermore, the Food and Drug Administration has approved several phosphorothioate antisense oligonucleotides for systemic administration to patients and for ex vivo treatment of hematopoietic stem cell grafts. These approvals include the now-completed OL(1)p53 phase I clinical trials (both systemic and ex vivo administered) which targeted transcripts of the p53 gene in patients with acute myeloid leukemia (Bayever et al., Antisense Res. Develop. 2: 109-110, 1992; Karp and Broder, Cancer Res. 54: 653-665, 1994). Thus, antisense oligonucleotides have the pharmacologic properties necessary for use as drugs.

Detailed Description Text (8):
The subject of the present invention is the nucleotide sequence of the disclosed oligos (listed in Tables 1 through 5) in association with a chemical backbone, the backbone selected from, but not limited to, a list consisting of the following types (reviewed in Neckers et al., Crit. Rev. Oncogen. 3: 175-231, 1992): phosphorothioates, dithioates, methylphosphonates, phosphodiesters, morpholino backbones, polyamide backbones, and any combination of the aforementioned backbone types, including, for example, phosphorothioate-capped phosphodiesters. The backbones may be unmodified, or they may be modified to incorporate a ribozyme structure, or a pendant group. Additionally, 2'-O-methyl (ribose-modified) oligos are suitable for the practice of the invention. The 2'-o-methyl sugar modification can be associated with any of the backbone linkages, including phosphorothioates, and the modification can be limited to the ends of the oligonucleotide. The oligos may also be associated with a carrier or vehicle such as liposomes or micelles, although other carriers could be used, as would be appreciated by one skilled in the art. Such carriers are used to facilitate the cellular uptake and/or targeting of the oligo, and/or improve the oligo's pharmacokinetic and/or toxicologic properties.

CLAIMS:

1. A modified oligonucleotide between 15 and 30 nucleotides in length, inclusive, having a sequence that specifically hybridizes in a human cell with a complementary sequence of a human MDR1 gene and allelic variants thereof to inhibit expression of a multidrug resistance phenotype exhibited by said cell, said complementary sequence being selected from the group consisting of SEQ ID Nos: 103, 104 and 105 and said modification being a backbone modification selected from the group consisting of dithioate, methylphosphonate, morpholino, polyamide, or any combination of said

modification.

6. A modified oligonucleotide between 15 and 30 nucleotides in length, inclusive, consisting of a sequence that specifically hybridizes in a human cell with a complementary sequence of a human MRP gene and allelic variants thereof to inhibit expression of a multidrug resistance phenotype exhibited by said cell, said complementary sequence being selected from the group consisting of Sequence ID Nos: 106, 107, 108 and 109 and said modification being a backbone modification selected from the group consisting of dithioate, methylphosphonate, morpholino, polyamide, or any combination of said modification.

11. A modified oligonucleotide between 17 and 30 nucleotides in length, inclusive, having a sequence that specifically hybridizes in a human cell with a complementary sequence of a human MDR1 gene and allelic variants thereof to inhibit expression of a multidrug resistance phenotype exhibited by said cell, said complementary sequence having the sequence of Sequence ID No: 102 and said modification being a backbone modification selected from the group consisting of dithioate, methylphosphonate, morpholino, polyamide, or any combination of said modification.